ISSWSH
International Society for the Study of Women's Sexual Health

HISTORY OF HORMONAL THERAPIES FOR THE TREATMENT OF GENITOURINARY SYNDROME OF MENOPAUSE

PART 1

Tuesday, November 8, 2022

This webinar is made possible by an educational grant provided by Millicent Services Inc.

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International Society for the Study of Women's Sexual Health

Moderator

Rachel Rubin MD, IF

Panelists

Irwin Goldstein, MD, IF

Noel Kim, PhD, IF

Tami Rowen, MD, MS, FACOG, IF

James Simon, MD, CCD, NCMP, FACOG, IF

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ISSWSH
International Society for the Study of Women's Sexual Health

ISSWSH is a multidisciplinary, academic, and scientific organization with the following purposes:

- **To provide** opportunities for communication among scholars, researchers, and practitioners about women's sexual function and sexual experience,
- **To support** the highest standards of ethics and professionalism in research, education, and clinical practice of women's sexuality, and
- **To provide** the public with accurate information about women's sexuality and sexual health

Publications

THE JOURNAL OF
SEXUAL MEDICINE

SOCIETY REPORT

International Society for the Study of Women's Sexual Health (ISSWSH) Review of Epidemiology and Pathophysiology, and a Consensus Nomenclature and Process of Care for the Manageme Genital Arousal Disorder/Genito-Pelvic Dysesthesia (F

Irwin Goldstein, MD,[1,2] Barry R. Komisaruk, PhD,[3] Caroline F. Pukall, PhD,[4] Andrew T. Goldstein, MD,[6] Sue W. Goldstein, BA, CSE,[2] Rose Hartzell-Cush Susan Kellogg-Spadt, PhD, CRNP,[7,8] Choll W. Kim, MD, PhD,[9] Robyn A. Jacko April Patterson, PT, MSPT,[11] Kenneth M. Peters, MD,[12] and James G. Pfaus

MAYO CLINIC

The International Society for the Study of Women's Sexual Health Process of Care for Management of Hypoactive Sexual Desire Disorder in Women

Anita H. Clayton, MD; Irwin Goldstein, MD; Noel N. Kim, PhD; Stanley E. Althof, PhD; Stephanie S. Faubion, MD; Brooke M. Faught, WHNP-BC; Sharon J. Parish, MD; James A. Simon, MD; Linda Vignozzi, MD; Kristin Christiansen, MD; Susan R. Davis, MBBS, PhD; Murray A. Freedman, MD; Sheryl A. Kingsberg, PhD; Paraskevi-Sofia Kirana, PhD; Lisa Larkin, MD; Marita McCabe, PhD; and Richard Sadovsky, MD

THE JOURNAL OF
SEXUAL MEDICINE

SOCIETY CONSENSUS STATEMENT

2015 ISSVD, ISSWSH, and IPPS Consensus Terminology and Classification of Persistent Vulvar Pain and Vulvodynia

Jacob Bornstein, MD, MPA,[1,*] Andrew T. Goldstein, MD,[2,*] Colleen K. Stockdale, MD, MS,[3] Sophie Bergeron, PhD,[4] Caroline Pukall, PhD,[5] Denniz Zolnoun, MD, MPH,[6] and Deborah Coady, MD,[7] On behalf of the consensus vulvar pain terminology committee of the International Society for the Study of Vulvovaginal Disease (ISSVD), the International Society for the Study of Women's Sexual Health (ISSWSH) and the International Pelvic Pain Society (IPPS)

MAYO CLINIC

CLINICAL PRACTICE GUIDELINES

REVIEW

The International Society for the Study of Women's Sexual Health Process of Care for the Identification of Sexual Concerns and Problems in Women

Sharon J. Parish, MD; Steven R. Hahn, MD; Sue W. Goldstein, BA; Annamaria Giraldi, MD, PhD; Sheryl A. Kingsberg, PhD; Lisa Larkin, MD; Mary Jane Minkin, MD; Vivien Brown, MDCM; Kristin Christiansen, MD; Rose Hartzell-Cushanick, PhD; Alyse Kelly-Jones, MD; Jordan Rullo, PhD; Richard Sadovsky, MD; and Stephanie S. Faubion, MD

REPORT

Genitourinary Syndrome of Menopause: New Terminology for Vulvovaginal Atrophy from the International Society for the Study of Women's Sexual Health and The North American Menopause Society

David J. Portman, MD,* Margery L.S. Gass, MD,† on behalf of the Vulvovaginal Atrophy Terminology Consensus Conference Panel

*Director, Columbus Center for Women's Health Research, Columbus, OH, USA; †Executive Director, The North American Menopause Society, Mayfield Heights, OH, USA

ICINE

SOCIETY REPORT

International Society for the Study of Women's Sexual Health Clinical Practice Guideline for the Use of Systemic Testosterone for Hypoactive Sexual Desire Disorder in Women

Sharon J. Parish, MD,[1] James A. Simon, MD,[2] Susan R. Davis, MBBS, PhD,[3] Annamaria Giraldi, MD, PhD,[4,5] Irwin Goldstein, MD,[6,7] Sue W. Goldstein, BA, CSE,[7] Noel N. Kim, PhD,[8] Sheryl A. Kingsberg, PhD,[9] Abraham Morgentaler, MD,[10] Rossella E. Nappi, MD, PhD,[11] Kwangsung Park, MD, PhD,[12] Cynthia A. Stuenkel, MD,[13] Abdulmaged M. Traish, PhD,[14] and Linda Vignozzi, MD[15,16]

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ISSWSH
International Society for the Study of Women's Sexual Health

Fall Course

2022

Scottsdale, AZ - USA

November 17-20, 2022

ISSWSH
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Genitopelvic Pain Course 2023

6x Virtual

Please visit www.isswshcourse.org/gpc for all the dates!

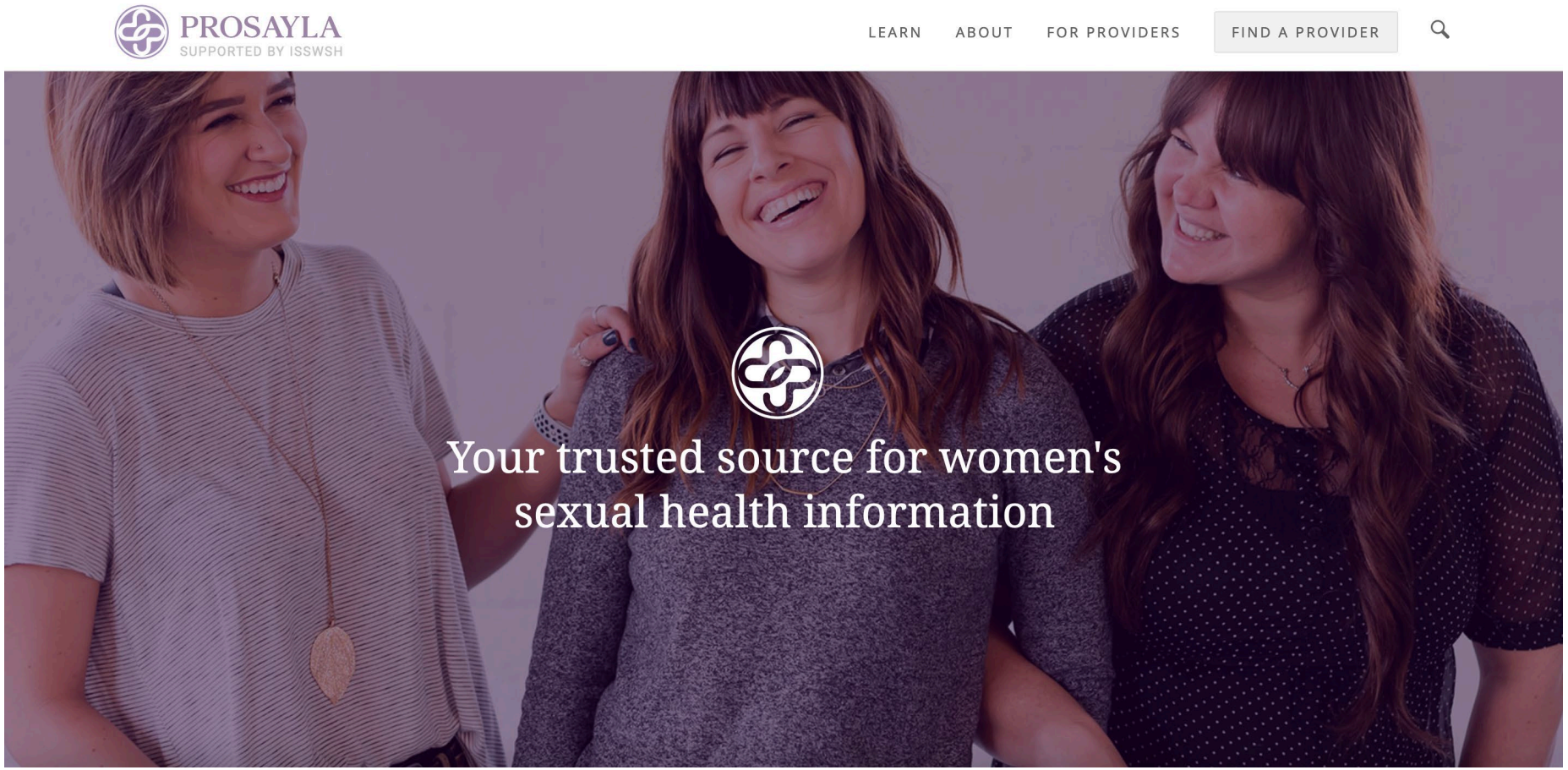
ISSWSH Annual Meeting 2023

March 2-5, 2023

ISSWSH
International Society for the Study of Women's Sexual Health

Marriott St. Louis Grand
St. Louis, MO, USA

Prosayla.com - patient information



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Everyone Deserves Sexual Health

- Learn about FSD
- Practice what you learn…one disease state at a time
- Help your patients…ethical thing to do…make a difference
- Be a lifelong learner…continue taking courses in women's sexual health….come back next year for more

For more information about ISSWSH:

https://www.isswsh.org

info@isswsh.org

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PART 1

INTRODUCTION OF ISSWSH AND FACULTY

Rachel Rubin, MD, IF

HISTORY OF TREATMENTS FOR VVA/GSM

Tami Rowen, MD, MS, FACOG, IF

PHYSIOLOGY OF THE VAGINA AND VESTIBULE: ESTROGENS AND ANDROGENS

Noel Kim, PhD, IF

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History of Treatments for GSM

Tami Serene Rowen MD MS IF FACOG
Associate Professor
University of California, San Francisco
San Francisco, CA

Disclosures

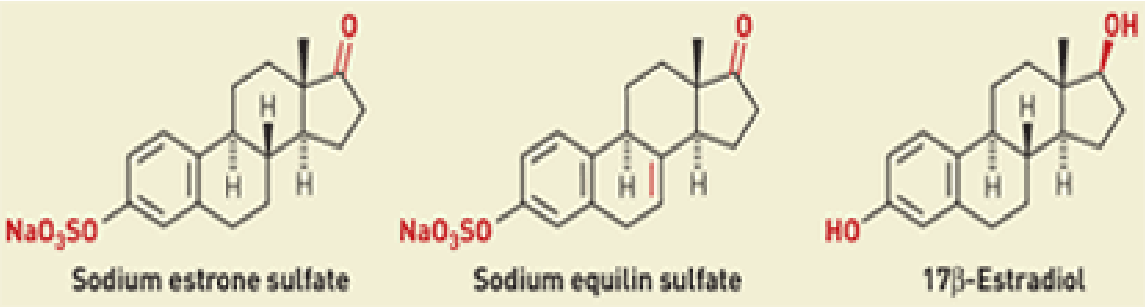
- Rosy Wellness

Introduction

- GSM treatments have been around for last 75 years
- Nearly all treatments initially indicated for atrophy alone for majority of time approved
  - Improving sexual health wasn't an indication until the 2010s!
- Progress in development of new delivery methods and gaining indications has been slow

Conjugated Equine Estrogen: the first

- Name “Premarin” was coined from pregnant mare urine, from which the estrogen complex was isolated
- Premarin is made of 10-50 different steroid hormones, mostly estrogens.
- The two key estrogens in Premarin are estrone sulfate (50 to 60%) and equilin sulfate (22.5 to 32.5%)

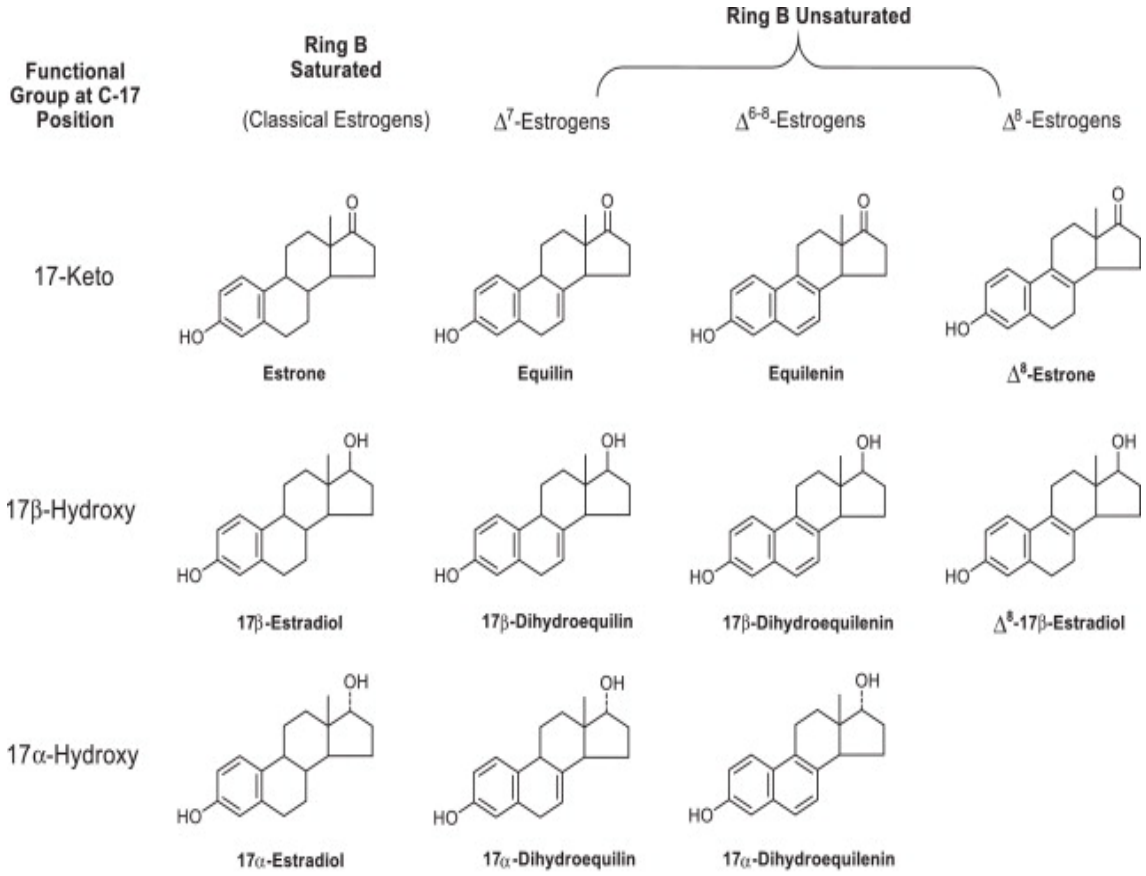


https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020216s083lbl.pdf

Vance DA Dph. Premarin: the intriguing history of a controverisal drug. Int J Pharm Compd. 2007 Jul-Aug;11(4):282-6. PMID: 23974785

Conjugated Equine Estrogen: cont…

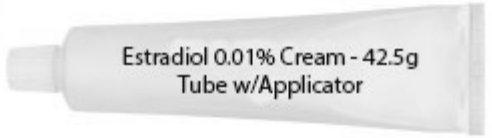
- Research started in the 1930s and oral Premarin was introduced in 1941
- Initial US approval of cream was 1946
- By 1992 Premarin was the #1 prescribed drug in the US
- There is still no generic!



https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020216s083lbl.pdf
Vance DA Dph. Premarin: the intriguing history of a controverisal drug. Int J Pharm Compd. 2007 Jul-Aug;11(4):282-6. PMID: 23974785

Estradiol Vaginal Cream

- Estradiol 0.01% vaginal cream

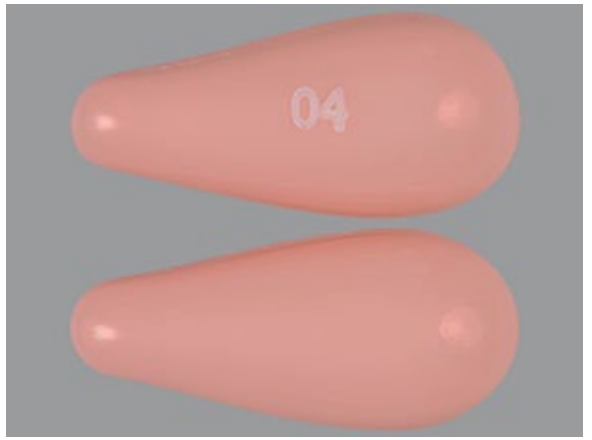


- Approved in 2001!
- This uses 17B estradiol, which is identical to the estradiol produced in the human ovary
- Indication again for GSM

Competition starts heating up

- Estradiol vaginal tablets initially introduced in 1998
  - 25 mcg
  - In effort to create lowest dose possible lead to development of 10 mcg pill
  - No statistical difference between 25 an 10, all better than placebo
  - Approved 2009

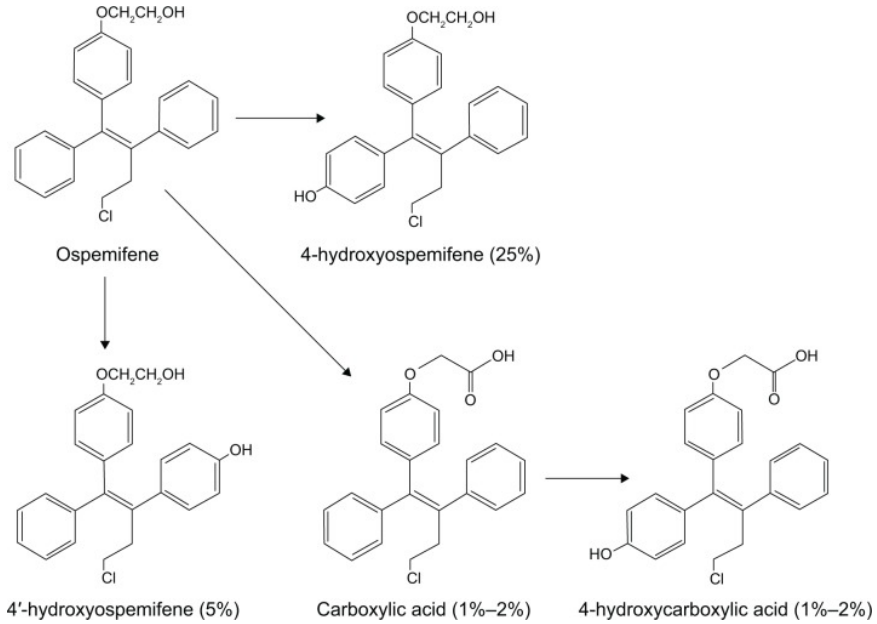
- Even lower dose tablets 4 mcg approved in 2018
  - Actually gets an “dyspareunia” indication



Chollet JA. Efficacy and safety of ultra-low-dose Vagifem (10 mcg). Patient Prefer Adherence. 2011.

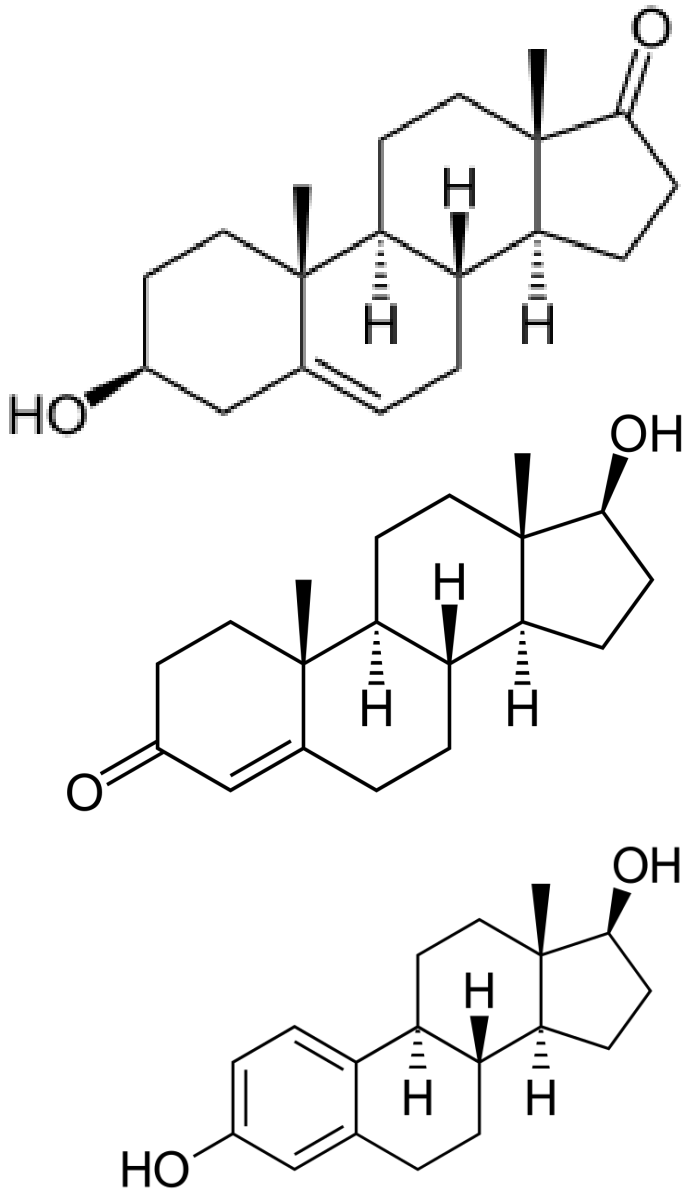
Speaking of Sex…

- It was actually Ospemefine, a systemic medication that was the first drug to get approved for “dyspareunia” (related to atrophy)
- 20 years of development, approval 2013
- Not an estrogen, it’s a SERM
- Unlike most SERMS, strong affinity for vaginal epithelium
- 52 week safety data showed no stimulation of endometrium
- Most common AE is hot flashes



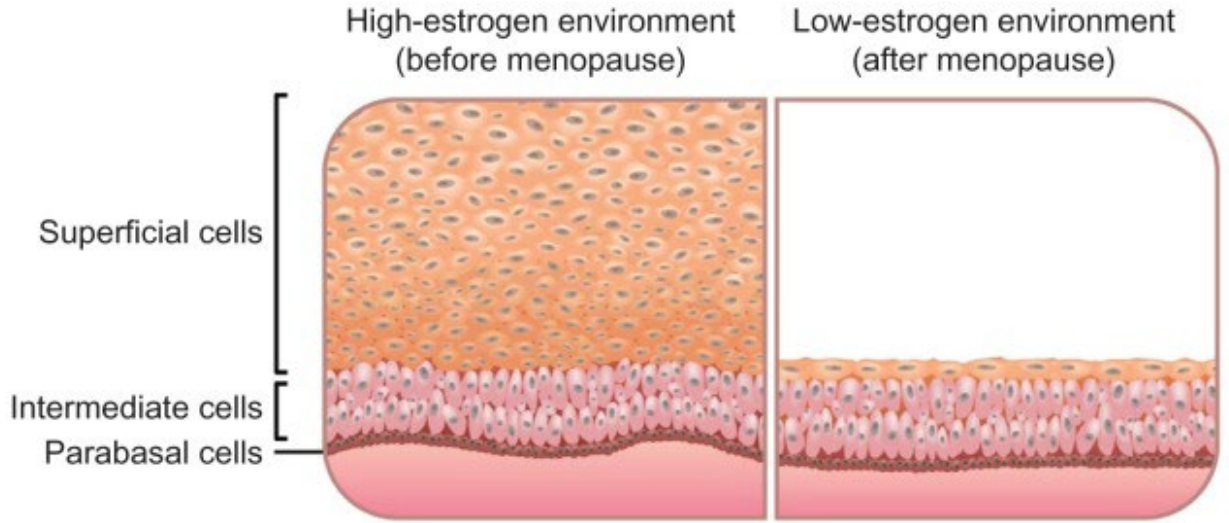
The last of the bunch… prasterone

- Approved November 2016
  - Indication: dyspareunia from atrophy
- “Non hormonal”
  - Pro/Pre-hormone
  - Metabolizes into testosterone and estradiol
  - Postmenopausal levels maintained during use
- Daily insert, different than the others…



Summary

- We have come a long way!
- Currently several products
- Most treatments still topical
- All treatments target the known steroid receptors that are most beneficial to vulva and vaginal health



Reiter, Suzanne. (2013). Barriers to effective treatment of vaginal atrophy with local estrogen therapy. International journal of general medicine. 6. 153-8. 10.2147/IJGM.S43192.

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Physiology of the Vagina and Vestibule: Estrogens & Androgens

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Disclosures

Consultant

- TriangleRX Consult
- Sprout Pharmaceuticals

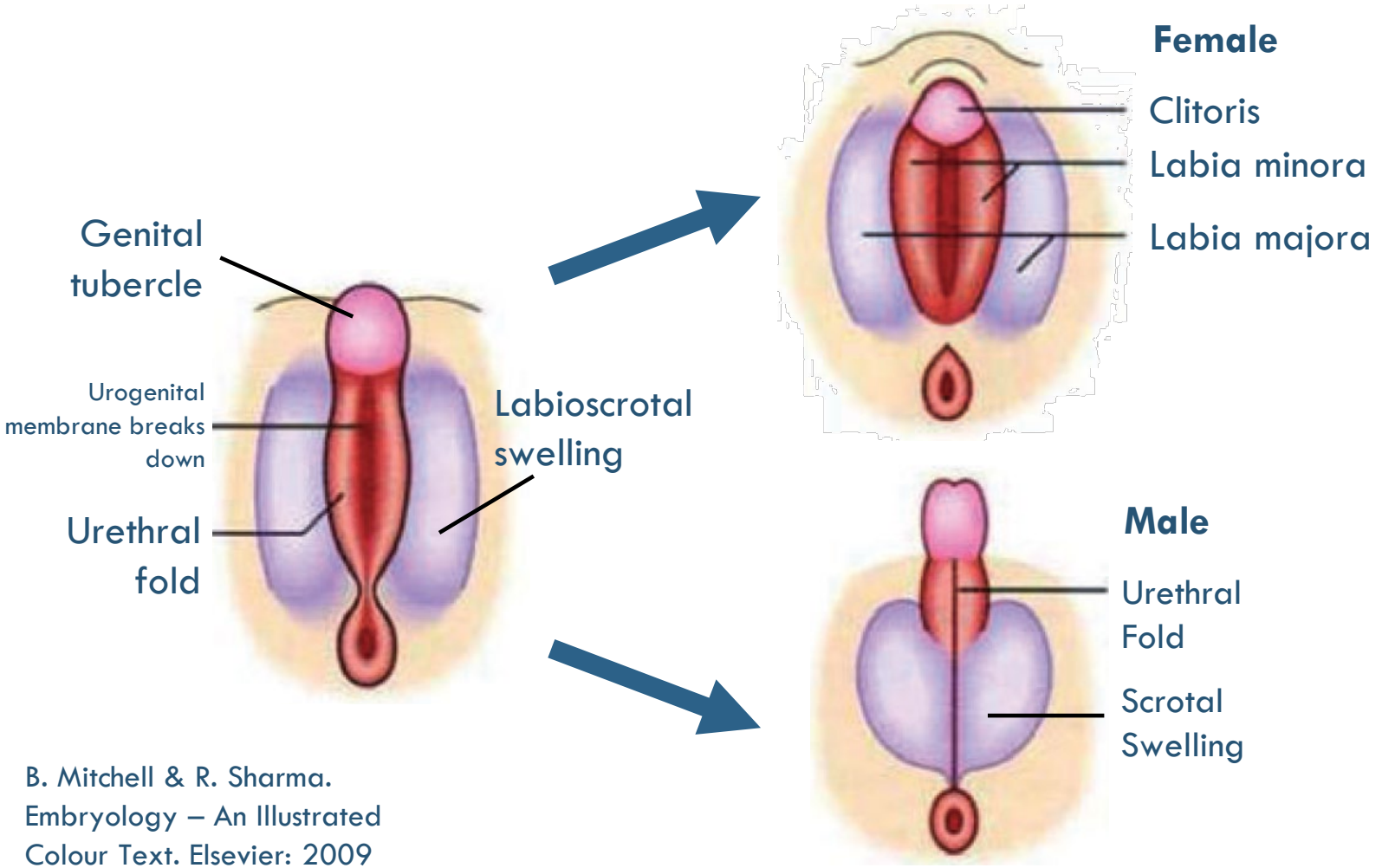
Advisory Board

- Genus Therapeutics

Development of Female Urogenital Tissues

- <u>Mesoderm</u>
  - vagina
  - uterus
  - smooth muscle of bladder
- <u>Endoderm</u>
  - vestibule & associated glands
  - urethra
  - urothelium

Development of External Genitalia



B. Mitchell & R. Sharma. Embryology – An Illustrated Colour Text. Elsevier: 2009

Vestibule – transition to increased AR expression in external genitalia of adults [Hodgins 1998]

AR distribution is identical in homologous tissues of both sexes in developing external genitalia [Kalloo 1993]

Distribution of ER & AR in Urogenital Tissue

- ER in vagina, vestibule, urethra, bladder, autonomic & sensory neurons
- Higher levels of AR in labial skin compared to vaginal epithelium
- AR present in mucin-secreting vestibular (Bartholin) glands
- ERα predominant in subdermal fibromuscular layer while AR in subdermal vascular layer

Hormonal Changes = Tissue Changes

	Estradiol	Testosterone
Early Childhood	< 13 pg/mL	< 20 ng/dL
Reproductive Years	40 - 350 pg/mL	20 - 70 ng/dL
Menopause	13 pg/mL	25 ng/dL

In utero → **Early Childhood** → **Reproductive Years** → **Menopause**

Trophic Effects of Androgens

- Positively correlated to urethrovaginal tissue volume in women
  [Battaglia et al. J Sex Med 2010;7:1445-53]
- Improved clitoral blood flow in women with FSD
  [Cipriani et al. J Endocrinol Invest 2021;44:2765-76]
- Wall thickness and growth factor expression in bladder (animal studies)
  [Yu et al. Urology 2009;73:1210-7]
- Maintains pelvic floor mass (animal studies) – clinical trial in process
  [Nnodim et al. 1999 & 2001 Anat Rec]

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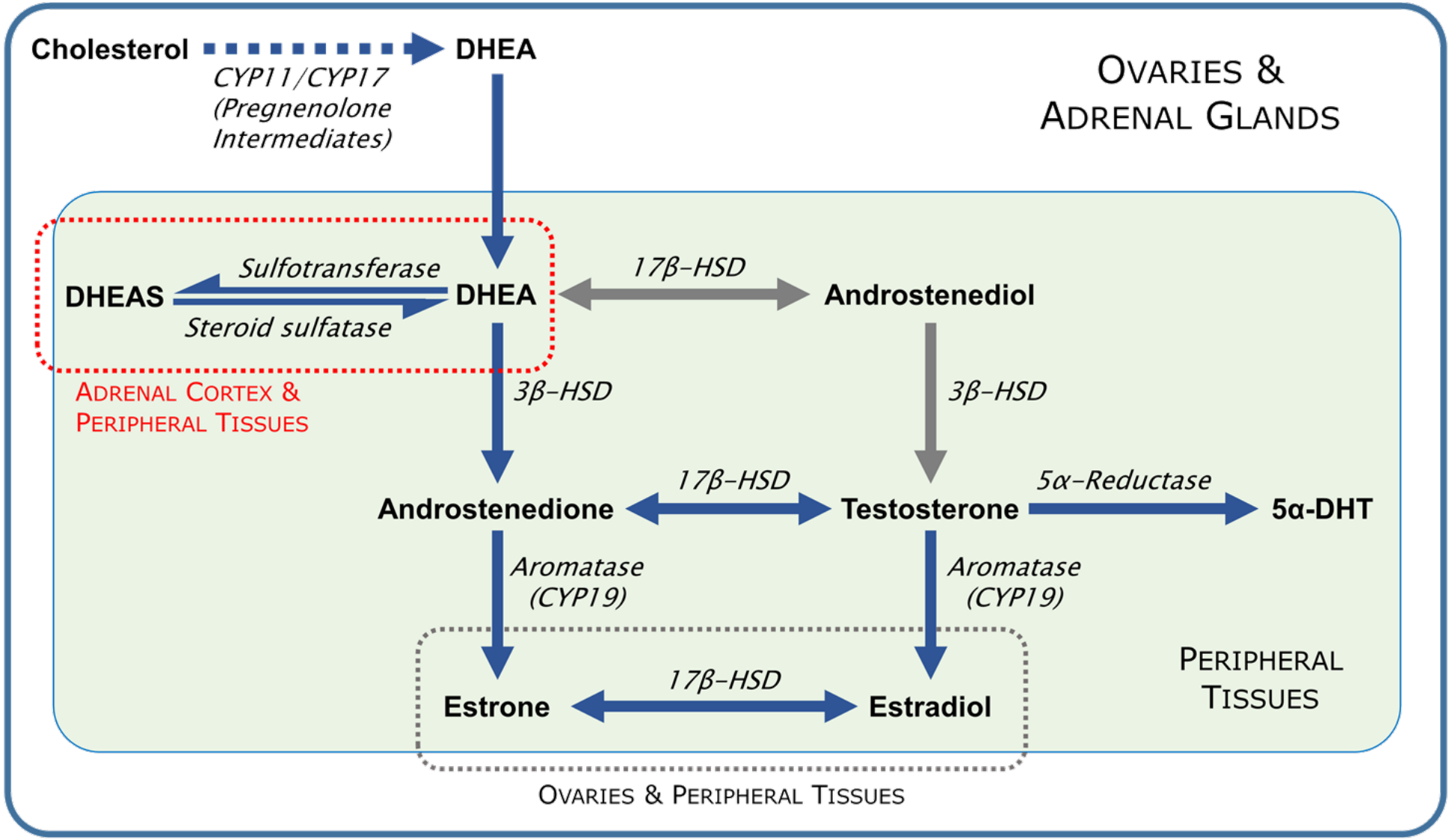

Parish et al. J Sex Med 2021;18;849-867

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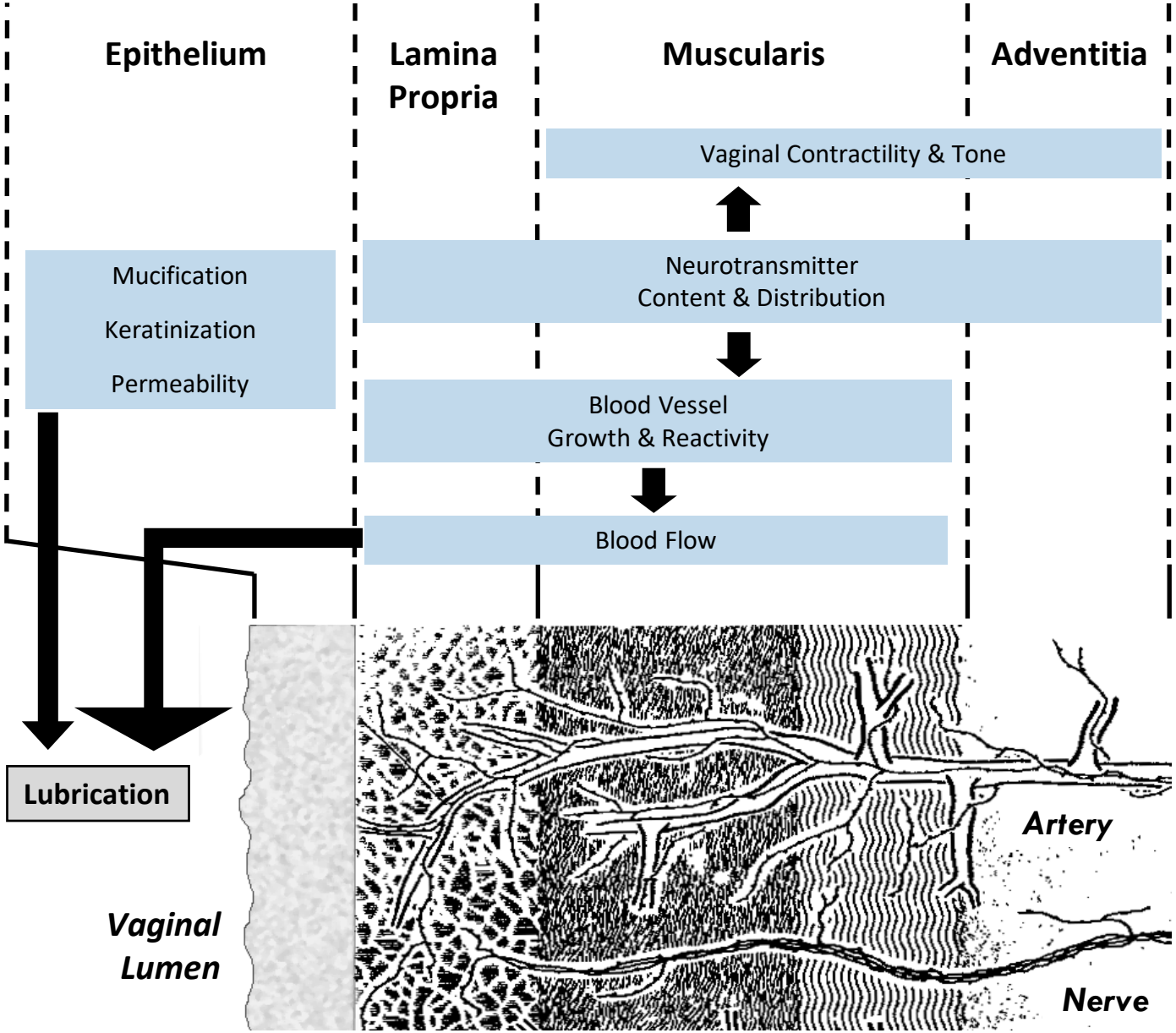
Local Synthesis of Hormones in the Vagina

- Intracrinology concept (Labrie) – mostly established with animal data (rodents & non-human primates) - little evidence in human tissues
- Aromatase mRNA detected in human vaginal tissue [Berman et al. Fertil Steril 2003;79:925]

Cellai et al. Endocrinol 2021;162:bqaa219

- Human vaginal smooth muscle cells in culture express mRNA for steroidogenic enzymes (isoforms of HSD, 5α-reductase, sulfotransferase)
- DHEA supplementation to cultured cells resulted in dose and time-dependent increases in Δ4-androstenedione, testosterone & DHT.
- mRNA for AR was expressed at higher levels than ERα, ERβ & PR

Vaginal Health Goes Beyond the Epithelium



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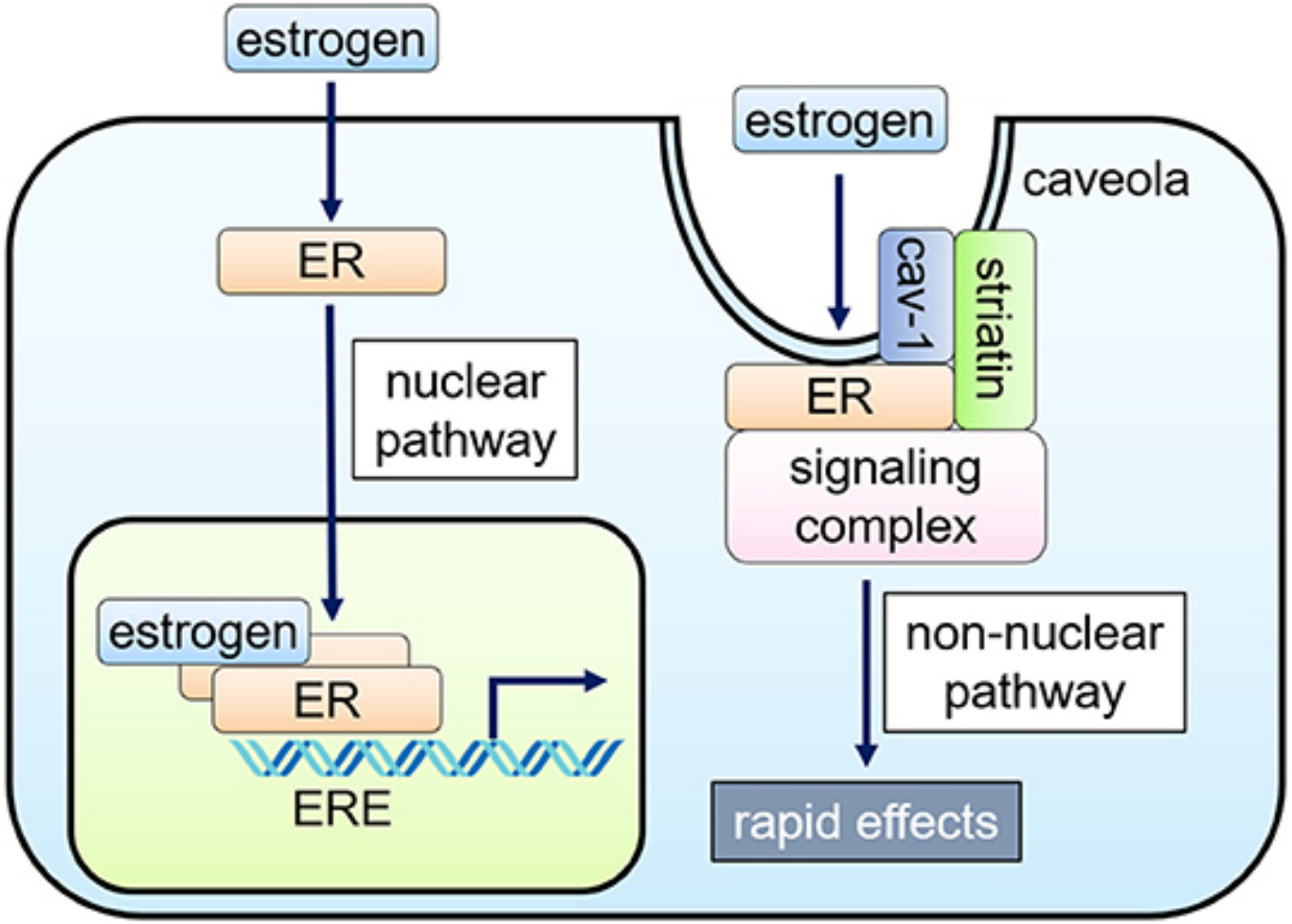
Estrogen Receptor Signaling



Ueda et al. Front Endocrinol 2020;10:909

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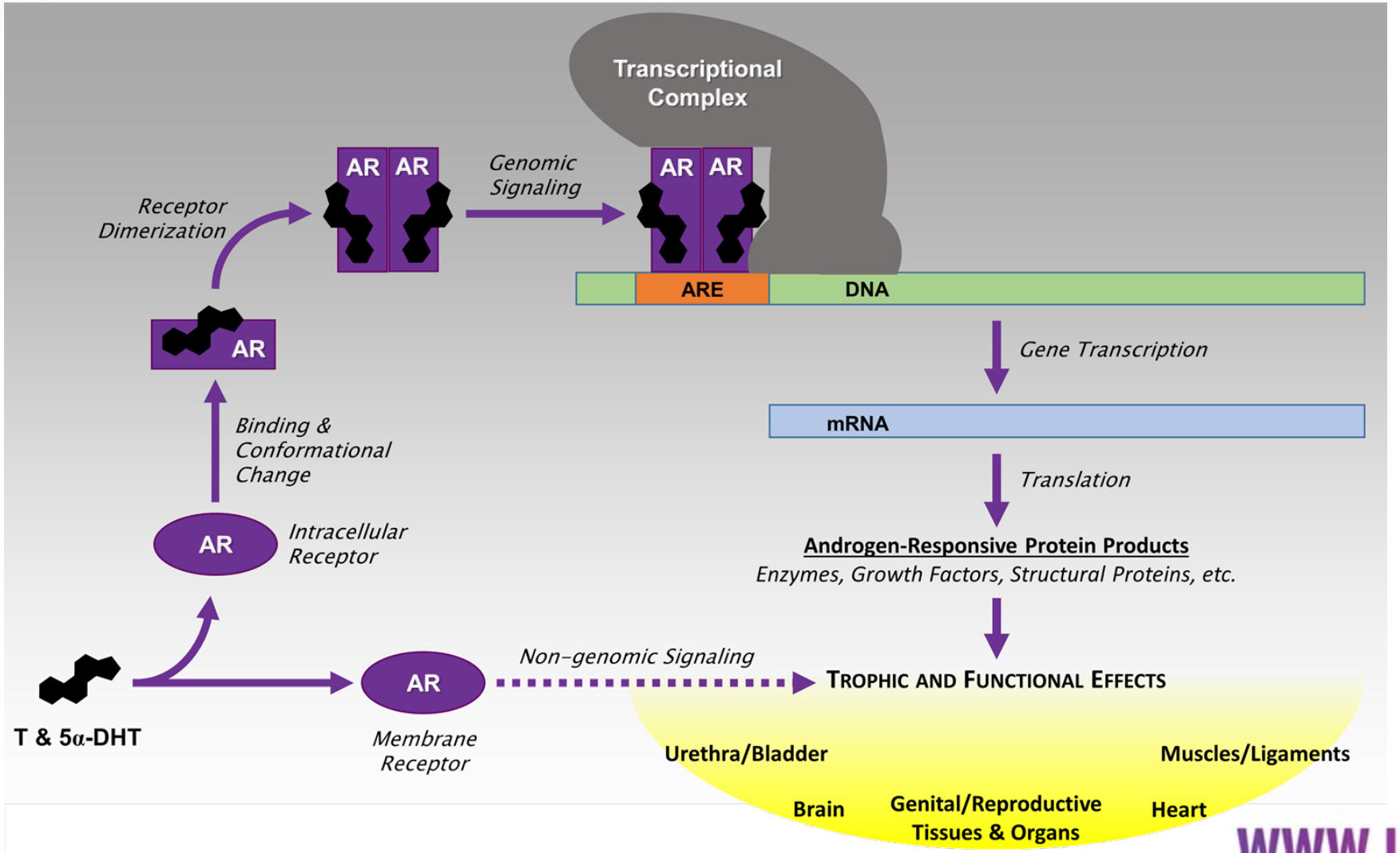
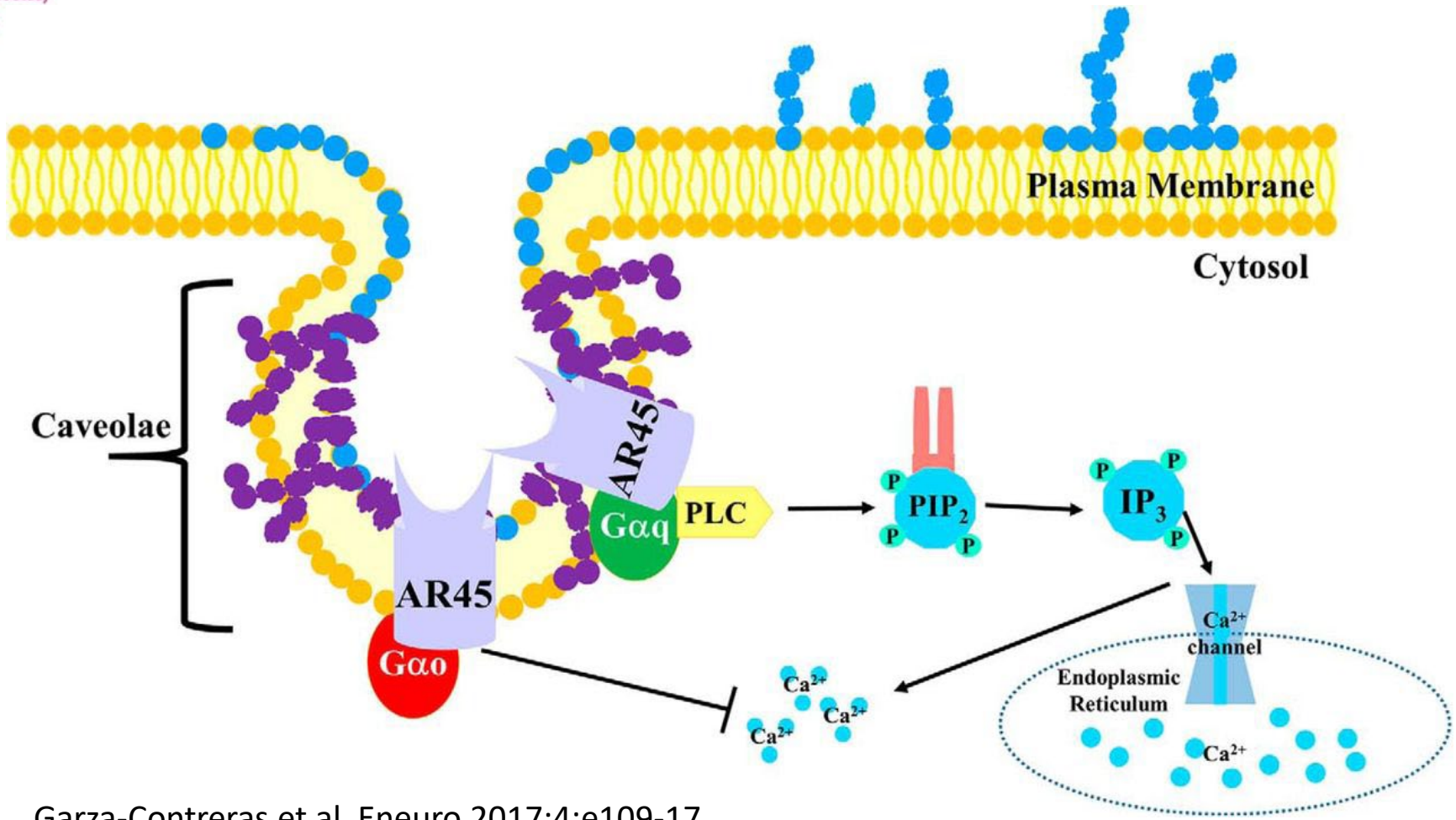
Androgen Receptor Signaling



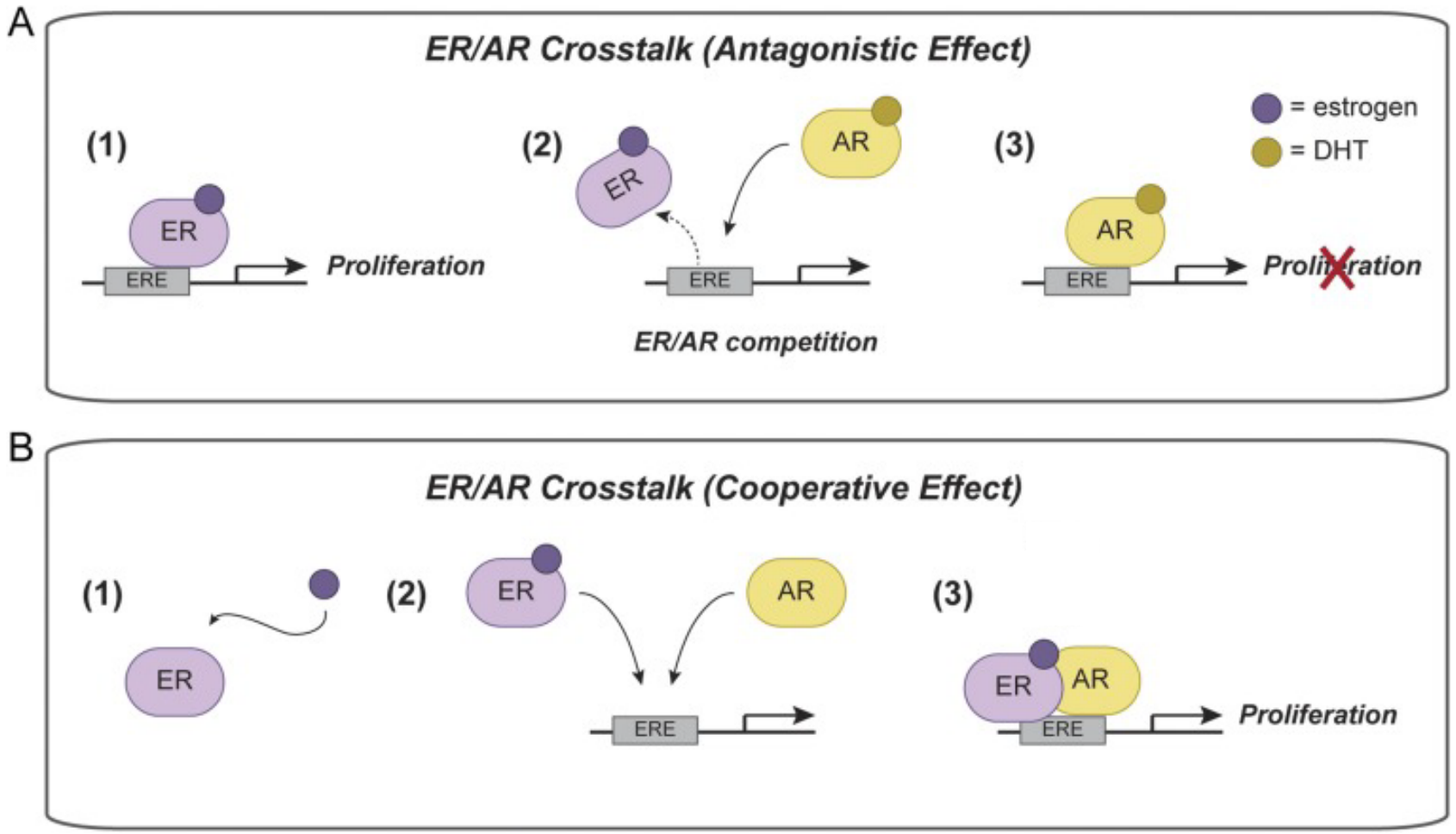
AR Signaling: Alternative Pathways



Garza-Contreras et al. Eneuro 2017;4:e109-17.

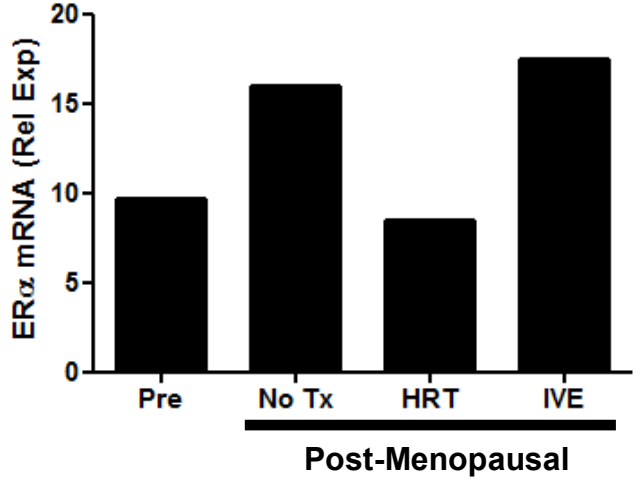
Crosstalk between Estrogen & Androgen Receptors

- Phosphorylation events can activate steroid receptors in absence of hormone
- Co-activators or transcription factors can interact with multiple steroid receptors
- Allosteric regulation of steroid receptors

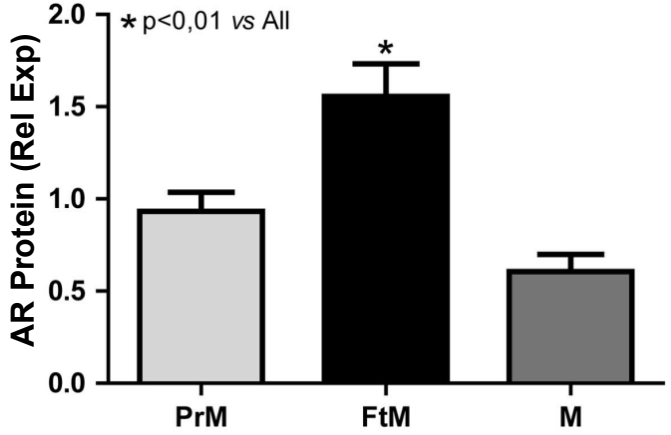


Regulation of ER & AR Expression in Women

- ERα mRNA increases in the vagina of post-menopausal women & decreases after systemic HRT, but not with intravaginal E_2 (Skala CE et al. *Eur J Obstet Gynecol Reprod Biol* 2010;153:99-103).



- AR protein levels increased in vagina of women treated with long-term, high dose testosterone when compared to pre- or post-menopausal women. (Baldasarre et al., Int J Impot Res 2013;25:7-11)



Role for Testosterone in Pain Modulation

- Testosterone may regulate serotonin transporter (SERT) in nucleus raphe magnus – increased levels of SERT associated with hyperalgesia of skeletal muscle

  [Lesnak et al. Pain 2020;161:2898-2908]

- Testosterone may increase estradiol in the CNS to stimulate endogenous opioid peptides (central desensitization)

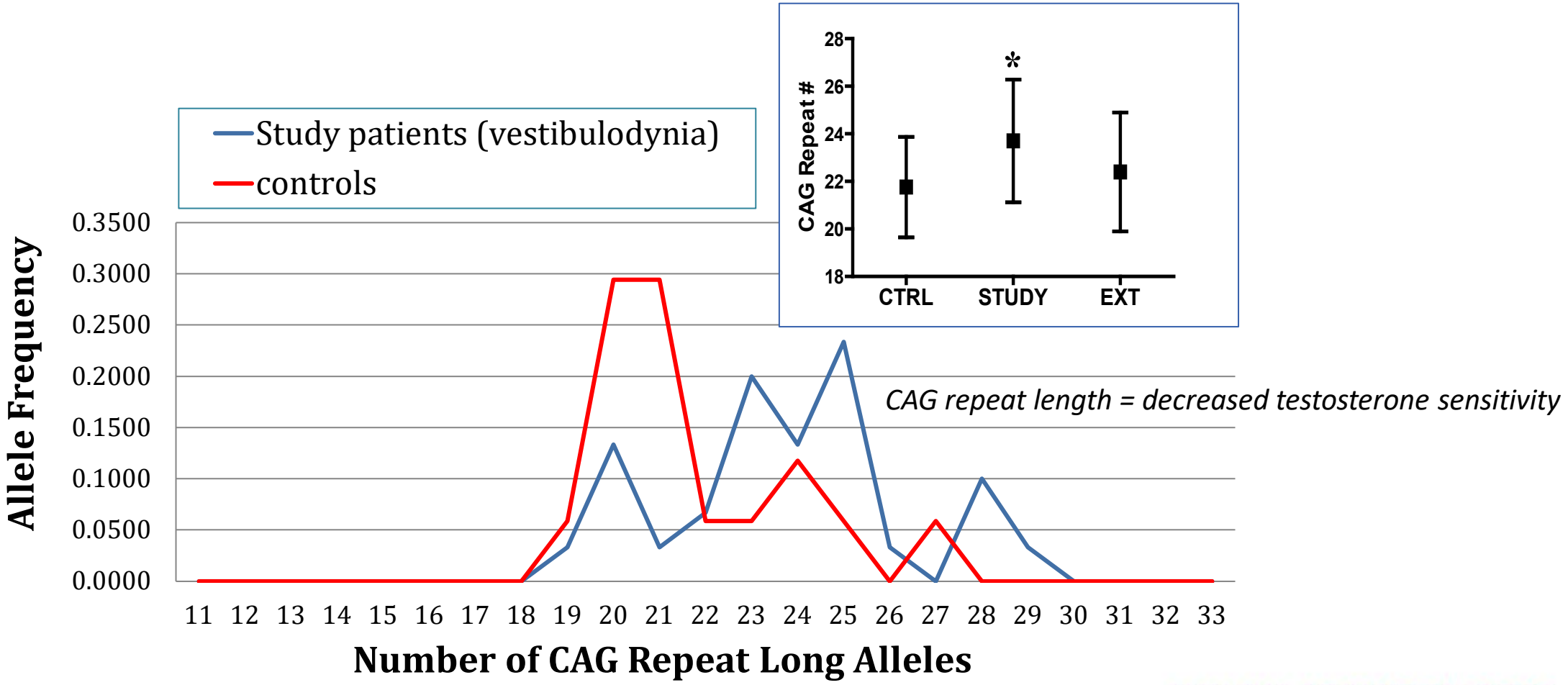
  [White et al. Int Immunopharmacol 2015;27:244-248]

Anti-inflammatory Effects of Testosterone

Maseroli et al. J Mol Endocrinol 2020;65:109-124

- Chronic inflammation may be involved in the underlying pathophysiology of GSM
- In cultures of human vaginal smooth muscle cells, DHT treatment decreased secretion of cytokines and growth factors:
  - basal secretion
  - LPS-stimulated secretion
  - IFNγ-stimulated secretion
- Effects of DHT were blocked by AR antagonist bicalutamide

Androgen receptor CAG repeat distribution is shifted toward longer repeat length in vestibulodynia patients



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